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10/001,267
Docket 093/004p

REMARKS

This paper is responsive to the Office Action dated March 9, 2004, which is the first action on the merits of the application.

Claims 13-28 were previously pending in the application and under examination. Upon entry of this Amendment, claims 29-40 are added. The added claims depend from claims previously considered, and fall within the group under examination. Accordingly, claims 13-40 are now pending in the application and under examination.

Further consideration and allowance of the application is respectfully requested.

Claim amendments:

Entry of the claim amendments does not introduce new matter into the disclosure. Support for the new claims may be found throughout the specification and claims as previously presented. New claims 29 and 30 are supported *inter alia* by Example 5, page 42 ff. New claims 29-30 are supported by claim 13 as previously presented. New claims 31-36 depend from claim 28, and echo claims 14, 15, 16 and 18 together, 20, 21, and 23. New claims 37-40 depend from claim 27, and echo claims 14, 15, 16 and 18.

No new limitation is added to claim 13 and its dependents. Accordingly, coverage is maintained for all equivalents of the claimed subject matter for which applicant was previously entitled. Claim 28 now recites hES cells rather than pPS cells. Coverage is maintained for all equivalents of hES cells for which applicant was previously entitled.

Double Patenting

The pending claims stand provisionally rejected for obviousness-type double patenting over certain claims of copending application USSN 10/087,142.

Applicant acknowledges this rejection. Upon indication of the subject matter otherwise patentable in this and the other application, applicant hereby undertakes to file a terminal disclaimer in one or the other application, or take other appropriate action to obviate double patenting.

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Rejection under 35 USC § 112 ¶ 1:

Claim 28 is rejected under § 112 ¶ 1 on the basis that the term *human embryonic stem (hES) cells* reads on totipotent cells. This rejection is not made against the other claims under examination, even though hES cells are an exemplary type of primate pluripotent stem (pPS) cells, as defined in the application. The Office Action states that the claimed differentiation method is enabled for pPS cells, but not totipotent cells. An academic paper by Pera et al. (J. Cell Sci. 113:5, 2000) is cited as standing for the proposition that only mouse ES cells have been shown to have four criteria of totipotent cells.

Applicant respectfully disagrees with this rejection. First of all, the invention claimed in this application is a *method* for differentiating cells. There are no claims to totipotent cells themselves, or a method of producing totipotent cells. Therefore the question of whether totipotent cells can be obtained is irrelevant to whether the invention meets the enablement requirements of § 112 ¶ 1.

The proper question is whether the method could be used to make hepatocytes from the cell types falling within the meaning of the starting cell population, when they are available. Whether the hES cells are totipotent or pluripotent, applicant does not see how this would affect the claimed method. The application provides working examples (page 36 ff.) that show how to make hepatocyte lineage cells using histone deacetylase inhibitors — using a starting stem cell population that meets all the definitions required in the specification for hES cells (page 9, lines 19-24). The Office Action does not explain why the method would fail if the hES cells were totipotent.

Secondly, applicant respectfully submits that it is treacherous and against public policy to speculate on whether hES cells obtained from human blastocysts as described in the specification are truly "totipotent". The hES cells used in the working examples are ES cells of the type described in U.S. Patent No. 6,200,806. Column 15, line 47 ff. of the '806 patent states the following:

The essential characteristics that define R278.5 cells as ES cells include: indefinite (greater than one year) undifferentiated proliferation in vitro, normal karyotype, and potential to differentiate to derivatives of trophectoderm and all three embryonic germ layers. In the mouse embryo, the last cells capable of contributing to derivatives of both trophectoderm and ICM are early ICM cells. The timing of commitment to ICM or trophectoderm has not been established for any primate species, but the potential of rhesus ES cells to contribute to derivatives of both suggests that they most closely resemble early totipotent embryonic cells. The ability of rhesus ES cells to form trophoblast in vitro distinguishes primate ES cell lines from mouse ES cells. Mouse ES cells have not been demonstrated to form trophoblast in vitro, and mouse trophoblast does not produce gonadotropin.

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According to the '806 patent, under certain conditions, cultured primate ES cells form trophoblast as well as cells from all three germ layers, which is *beyond the capability of mouse ES cells*. But according to the Pera reference, mouse ES cells are the one type of cells that has been shown to meet the four criteria of totipotent cells.

Following the reasoning given in the Office Action, in order to fulfill the criteria of a totipotent cell, someone will have to make germline tissue or a whole animal (bottom of Page 4). The implication is that hES cells are not known to be totipotent cells *because nobody has tried to make a whole human from a human embryonic stem cell line*.

Applicant respectfully submits that no limitation should be made to the claim, either directly or by way of the file history, to imply that the claimed method cannot be used with totipotent hES cells. To do so would open up the possibility that someone could work around the patent by showing that the hES cell line they were using to make hepatocytes was in fact a totipotent cell line. This might create an incentive for someone to make a human being from hES cells. Surely this is contrary to the policy and good sense of the U.S. Patent and Trademark Office.

Withdrawal of this rejection is respectfully requested.

Rejection under 35 USC § 112 ¶ 2:

Claims 13 and 28 stand rejected under this section for referring to the culturing of pPS or hES cells and "their progeny".

The claims were worded using this term to accommodate the options of either:

- adding the histone deacetylase inhibitor to the hES cells in the undifferentiated state (Example 5, page 42 ff.) so as to guide the cells into the hepatocyte pathway immediately; or alternatively,
- initiating a general (non-specific) differentiation process, and then directing the imitated cells into the hepatocyte pathway by adding the histone deacetylase inhibitor to the initiated cells (Example 1 and Example 9; claims 19 and 20).

The claims have now been reworded to eliminate reference to "progeny", and refer to the option of initiating differentiation more explicitly. Use of an optional step in this fashion complies with the requirements of § 112 ¶ 2 as indicated in MPEP § 2173.05(h)(III), since the alternatives are clearly to conduct steps a), b), and c), or to conduct steps a) and c) only. Methods of initiating differentiation are

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exemplified in claims 19 and 20. The option of omitting the imitation step is explicitly covered in new claim 29.

Withdrawal of this rejection is respectfully requested.

Information Disclosure Statement

Applicant is grateful to the Examiner for considering the information provided in the preceding Information Disclosure Statement.

A further IDS under 37 CFR § 1.97(c)(2) along with the requisite fee is being filed under separate cover. The Examiner is asked to consider the new references and make them of record in this application.

Request for Interview

Applicant respectfully requests that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

In the event that the Examiner determines that there are other matters to be addressed, applicant hereby requests an interview by telephone.

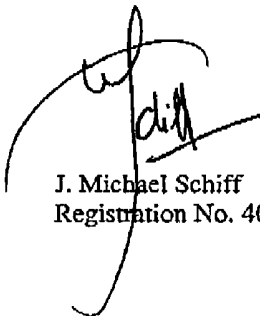
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Fees Due

Enclosed with this Amendment is authorization to charge the Deposit Account for the new claims.

Should the Patent Office determine that a further extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief, and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "J. Michael Schiff", is written over a large, stylized, handwritten letter "J" that spans the signature and extends downwards.

J. Michael Schiff
Registration No. 40,253

GERON CORPORATION
230 Constitution Drive
Menlo Park, CA 94025
Telephone: (650) 473-7715
Fax: (650) 473-8654

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